

Docket No.: 067234-0056

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK EXAMINER  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of CHEE, Mark S., et al.	:	Customer Number: 41552
Application No.: 09/513,362	:	Confirmation Number: 7034
Filed: February 25, 2000	:	Tech Center Art Unit: 1637
Examiner: STRZELECKA, T.	:	
For: NUCLEIC ACID SEQUENCING USING MICROSPHERE ARRAYS	:	

**REPLY BRIEF TRANSMITTAL**

**CERTIFICATE OF ELECTRONIC TRANSMISSION**

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/Carrie Hines/

Sir:

Carrie Hines

Submitted herewith is Appellant's Reply to the Examiner's Answer mailed March 17, 2008. To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due under 37 C.F.R. §§ 1.17 and 41.20, and in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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**REPLY BRIEF TO EXAMINER'S ANSWER**

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/Carrie Hines/

Carrie Hines

This Reply Brief is submitted pursuant to Notice of Appeal filed on November 30, 2007.  
Appellants are separately filing a Request for Oral Hearing pursuant to 37 C.F.R. §41.47.

I. REMARKS

A. THE EXAMINER'S RESPONSE TO APPELLANTS' ARGUMENTS ON APPEAL

Appellants maintain their positions set forth in the Appeal Brief filed December 16, 2007. The following remarks are intended to supplement the comparatively more detailed arguments presented in the Appeal Brief without reiterating each position in its entirety.

**(1) The Examiner's Rationale for Combining the Particular Elements Lacks As Much As A Mention of the Particular Element of Pyrophosphate Sequencing.**

Appellants maintain that the appealed obviousness rejection lacks any articulated reason for using the claimed element of microspheres in combination with the claimed element of pyrophosphate sequencing and, therefore, fails to build a proper a prima facie case. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007) requires that an Examiner provide "some articulated reasoning with some rationale underpinning to support the legal conclusion of obviousness." 127 S.Ct. at 1741. An Examiner must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine **the elements in the way the claimed new invention** does," Id. Anything less than an articulated analysis is insufficient to support a prima facie case of obviousness.

The Examiner's Answer attempts to rebut Appellants' arguments that no articulated reasoning has been presented to date on the record by quoting the following pro forma sentence from a previous Office Actions, presumably to show that the case for motivation that has been articulated does include the particular method of pyrophosphate sequencing of Rothberg et al.:

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to **have used the microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid sequencing of Rothberg et al.**

Examiner's Answer, p. 18, second complete paragraph.

Appellants have consistently maintained that, in view of the particular characteristics of pyrophosphate sequencing, a reason to combine the two references is lacking and requested on

1 numerous occasions that the Examiner articulate the reason to combine **pyrophosphate**  
2 sequencing with beads. It speaks for itself that the Examiner's discussion of the problem  
3 addressed by the skilled person combining the cited references, which in its entirety amounts to  
4 the above-quoted general sentence and two paragraphs copied from Walt et al., does not even  
5 mention the term "pyrophosphate sequencing." A discussion of whether the combination was  
6 obvious to a person with ordinary skill in the art based on any need or problem known in the field  
7 and addressed by the claimed elements so as to provide a reason for combining the elements in  
8 the manner claimed must necessarily include a discussion, or at least would be expected to at least  
9 mention the particular elements themselves. In other words, "the method of nucleic acid  
10 sequencing of Rothberg et al." without further description of its particular features (which  
11 Appellants have addressed over and over on the record as impacting this obviousness analysis),  
12 represents boilerplate language that could be referring to any sequencing method and is entirely  
13 lacking in the requirement of particularity. While KSR "counsels against applying the [TSM test]  
14 as a rigid and mandatory formula... it remains necessary to show 'some articulated reasoning  
15 with some rational underpinning to support the legal conclusion on obviousness.'" Aventis Pharma  
16 v. Lupin (citing KSR v Teleflex). The Patent and Trademark Office's own guidelines for  
17 Examiners are in accord:

18       The key to supporting any rejection under 35 U.S.C. 103 is the **clear articulation**  
19       of the reason(s) why the claimed invention would have been obvious. The  
20       Supreme Court in KSR noted that the analysis supporting a rejection under 35  
21       U.S.C. 103 should be made explicit. The Court quoting In re Kahn stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'"

22       Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the  
23       Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57, 526 (2007)  
24       ("Guidelines") (emphasis added).

25       The Examiner now defends her lack of mentioning pyrophosphate sequencing in her construction  
26       of a prima facie case by stating that "one skilled in the art would not need any further explanatory  
27       comments added." Examiner's Answer, p. 18. It is respectfully submitted that a clear articulation  
28

of why the claimed invention is considered obvious by showing that there existed a known problem for which Rothberg et al. and Walt et al. provided an obvious solution that corresponds to the claimed invention is not possible without discussing the particular claim element of pyrophosphate sequencing.

**(2) The Examiner's Answer Mischaracterizes Rothberg et al.'s "Teaching Away"**

While the Examiner concedes that that Rothberg et al. do not teach using beads as solid support, she disputes that Rothberg et al. "teach away" and provides her analysis of Rothberg et al. at Column 21, lines 15-34 (emphasis added):

Solid-phase pyrophosphate sequencing was initially developed by combining a solid-phase technology and a sequencing-by-synthesis technique utilizing bioluminescence (see e.g., **Ronaghi, et al., 1996. Real-time DNA sequencing using detection of pyrophosphate release. Anal. Biochem. 242: 84-89**). In the solid-phase methodology, an immobilized, primed DNA strand is incubated with DNA polymerase, ATP sulfurylase, and luciferase. By stepwise nucleotide addition with intermediate washing, the event of sequential polymerization can be followed. A remarkable increase in signal-to-noise ratio was obtained by the use of .alpha.-thio dATP in the system. This dATP analog is demonstrated to be efficiently incorporated by DNA polymerase while being silent for luciferase, allowing the sequencing reaction to be performed in real-time. **In these early studies**, sequencing of a PCR product using streptavidin-coated magnetic beads as a solid support was presented. However, it was found that the loss of the beads during washing, which was performed between each nucleotide and enzyme addition, was the limiting factor to sequence longer stretches.

In her answer, the Examiner, at page 20, first full paragraph, asserts the following as the "only conclusion" capable of being drawn in the above quote:

[T]he loss of beads in homogenous assays (where beads are suspended in solution) prevented sequencing of 'longer stretches' in this case tens, hundreds or thousands of base pairs. However, Appellant's [sic] claims are not drawn to sequencing of any particular lengths of nucleic acids.

There are two errors in the Examiner's assertion.

First, Appellants respectfully ask that the Board review the paragraph above, which is the subject of the Examiner's assertion. It is respectfully submitted that a review of the above-quoted excerpt from Rothberg et al. shows that the assertion that the paragraph is limited to assays where beads are suspended in solution is plain and simple incorrect on its face.

**(3) The Examiner’s Rebuttal of Appellants’ “Teaching Away” Argument Disregards Basic Rules of Claim Interpretation**

The second error in the Examiner’s assertion is that the teaching away applies only to stretches longer than tens of base pairs and, therefore, is outside the scope of the claims because the claims do not recite a particular length limitation. This assertion clearly runs afoul of basic claim interpretation. By virtue of not reciting “any particular lengths” the claims broadly encompass any length, including longer stretches of tens of base pairs. Accordingly, the teaching away by Rothberg et al. of anything longer than “tens of base pairs” is a teaching away from a vast proportion of what is encompassed by the claimed scope. A person of ordinary skill in the art would consider the above-quoted paragraph a “teaching away” from the invention as claimed given that the overwhelming majority of species of lengths encompassed by the claimed scope are predicted by Rothberg et al. to be inoperable in a method that combines pyrophosphate sequencing and beads. Viewed in light of what is the actual claimed scope, the Examiner’s assertion thus supports Appellants’ “teaching away” argument with regard to Rothberg et al.

The Supreme Court in KSR discussed in some detail United States v. Adams, 383 U.S. 39 (1966), stating in part that in that case, “[t]he Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious.” 127 S.Ct. at 1740. Accordingly, if such teachings are present and are significant, there may be no reason to make the asserted combination. As described in detail in the Appeal Brief filed December 16, 2007, Rothberg et al. explicitly teaches away from using beads as an array support in pyrophosphate sequencing reactions. Appeal Brief filed December 16, 2007; at VII.B.2.b. The mere identification of using beads by Walt et al. does not overcome this teaching away and the skilled person would have had no reason to make the claimed combination.

**(4) If Ronaghi et al. Provided The Solution to Bead Loss, Rothberg et al. Would Not Have Cited Ronaghi et al. As Representing The Problem**

1 The Examiner further asserts that the lack of a teaching away based on bead loss is somehow  
2 mitigated by the Ronaghi et al. reference, which is alleged to acknowledge as well as provide a  
3 solution to the problem of bead loss. Examiner's Answer, p. 20, starting at second complete  
4 paragraph. From a procedural standpoint, Appellants point out that Ronaghi et al. is not cited as  
5 prior art supporting the rejection and, therefore, Rothberg et al. and Walt et al. must be sufficient  
6 to render the claims obvious without a further reference that may or may not overcome the  
7 "teaching away" in Rothberg et al. The Examiner's citation to Ronaghi et al. to provide a  
8 combination of references that, along with Rothberg et al. and Walt et al. would be sufficient  
9 reason for the skilled person to combine the elements presently claimed, represents an implicit  
10 admission that Rothberg et al. and Walt et al., without more, cannot support this rejection.

11 On a more substantive point, we have clear evidence that, although Rothberg et al. were very  
12 familiar with Ronaghi et al.'s paper, Rothberg et al. did not share the Examiner's view that  
13 Ronaghi et al. provides a solution to the problem of bead loss. To the contrary, when Rothberg et  
14 al. explicitly point to reported problems associated with the use of pyrophosphate sequencing in  
15 combination with microspheres they do so in the context of their characterization of Ronaghi et  
16 al. (see emphasis added, supra, at page 3:10-17, which reproduces the entire paragraph:

17  
18 **In these early studies**, sequencing of a PCR product using streptavidin-coated  
19 magnetic beads as a solid support was presented. However, it was found that the  
20 loss of the beads during washing, which was performed between each nucleotide  
21 and enzyme addition, was the limiting factor to sequence longer stretches.

22 Column 21, lines 28-34. As becomes evident upon reading the entire paragraph, quoted supra, at  
23 p. 3:10-17 (with reference to Ronaghi et al. emphasized in bold type face), when Rothberg et al.  
24 refer to "these early studies" that showed bead loss as an impediment to sequencing of longer  
25 stretches, the authors were in actuality citing to the very Ronaghi et al. reference alleged by the  
26 Examiner to provide a solution to bead loss. Thus, rather than mitigating Rothberg et al.'s  
27 teaching away, the reference to Ronaghi et al. bolsters Appellants' argument. That is, Rothberg et  
28 al., although aware of Ronaghi et al. and its alleged solution to bead loss problem, explicitly

referred to the Ronaghi et al. reference in the context of teaching away from combining beads and pyrophosphate sequencing.

**(5) THE EXAMINER’S REBUTTAL OF CORROBORATING EVIDENCE PROVIDED BY ROTHBERG ET AL. DURING PROSECUTION OF THE CIP APPLICATION IS CONTRADICTED BY THE RECORD**

Another issue raised in the Examiner’s answer is the argument that bead loss was not an issue on which Rothberg et al. based the patentability of their continuation-in-part application of the ‘320 patent. Examiner’s Answer, p. 22, third paragraph to page 24, first complete paragraph. The Examiner quotes a number of paragraphs from Declarations submitted by Dr. Margulies during prosecution of the CIP and concludes that

It was the combined evidence of the influence of the well depth on the quality of the sequencing product, not evidence of bead loss that persuaded the Examiner to allow the Rothberg et al. case.

Examiner’s Answer, p. 24, first complete paragraph.

In view of the fact that the Board will review the relevant passages of the Examiner’s Answer, including the quotes from the Margulies Declarations as well as Appellants Opening Brief at VII.B.2.c, it is respectfully submitted that the record will speak for itself. What is apparent and safely concluded from the excerpts reproduced both in the Appeal Brief and the Examiner’s Answer is that the Rothberg et al. inventors expressed their view of bead loss as a problem in pyrosequencing methods in the cited ‘320 patent and further expressed their view that improvements to invention of the ‘320 patent captured in the CIP include parameters aimed at addressing, *inter alia*, the prior problem of bead loss in their pyrosequencing methods. Furthermore, in the above cited quote, the Examiner draws a conclusion as to what “persuaded the Examiner” of the Rothberg et al. CIP to allow this case based on quotes entirely based on the Margulies Declarations. It is respectfully submitted that the statements made on the record by the Rothberg et al. CIP’s Examiner himself should be uniquely relevant if the argument is based on his state of mind on the evidence of bead loss. Significantly, the Examiner’s Reasons for



1 Allowance establish the incorrectness of the assertion that bead loss was not a persuasive issue in  
2 allowing the Rothberg et al. CIP:

3 The diameter range, the depth, and **well-depth** of the claimed caviated fiber optic  
4 wafer . . . are deemed non-obvious over the general teaching provided for by Chee  
5 et al. (of record), based on Margulies Declaration, **as each of the above-**  
6 **mentioned parameters are critical to the laminar flow of the reaction reagents**  
7 **. . . (see page 3 bottom paragraph to page 4, top paragraph; Margulies**  
8 **Declaration).**

9 Notice of Allowability mailed February 7, 2007, at page 2 (emphasis added). Attached as Exhibit  
10 B to Appellants' Response filed March 8, 2007. The paragraph cited by the Examiner "**page 3**  
11 **bottom paragraph to page 4, top paragraph; Margulies Declaration**" as attesting why well-  
12 depth is a "**critical**" parameter:

13 [T]he claimed parameters for well diameter . . . and well depth . . . are not  
14 arbitrarily chosen parameters. Well depth is selected on the basis of a number of  
15 competing requirements in a nucleic acid sequencing application: **(1) wells need**  
16 **to be deep enough for DNA-carrying beads to remain in the wells . . .**

17 Exhibit E to Appellants' Response filed March 8, 2007, Margulies Declaration executed  
18 December 22, 2006, at para. 8, spanning pages 3 and 4.

19 Overall, in view of the above, it is respectfully submitted that prior to Appellants' filing date bead  
20 loss was perceived by the Rothberg et al. inventors as a problem and yet after Appellants' filing  
21 date overcoming the problem of bead loss was unquestionably perceived as an improvement of  
22 the CIP invention both by the Office's and the Rothberg et al. inventors. Thus, Appellants  
23 maintain that the record in the CIP application provides evidence that strongly corroborates  
24 Appellants' showing that the Rothberg et al. '320 patent teaches away from the use of beads in a  
25 pyrosequencing method.

26 **(6) WHETHER OR NOT APPELLANTS' DISCLOSURE IDENTIFIES AND ADDRESSES PROBLEMS**  
27 **ENCOUNTERED BY THE CITED PRIOR ART IS IRRELEVANT TO THE QUESTION OF OBVIOUSNESS**  
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1 Finally, the Examiner faults Appellants for not providing a solution to the problem of bead loss:

2       Considering all the emphasis Appellant placed on bead loss during the sequencing  
3       process, it seems like a gravely serious issue, and surely Appellant would provide  
4       a solution to the problem.

5 Examiner's Answer, pp. 24-25. Appellants respectfully submit that the prior art determination of  
6 whether or not bead loss is addressed in the context of teaching away from the combination of  
7 Rothberg at al. and Walt et al. to render obvious the claimed combination does not properly  
8 include Appellants' specification and its teachings.

9 The path that leads an inventor to the invention is expressly made irrelevant to patentability by  
10 statute. *See Life Technologies Inc.v. Clontech Lab, Inc.*, 224 F.3d at 1325, 56 U.S.P.Q.2d at 1190  
11 (Fed. Cir. 2000) (citing 35 U.S.C. § 103(a) and stating that "[i]t does not matter whether the  
12 inventors reached their invention after an exhaustive study of the prior art, or developed [their  
13 invention] in complete isolation.") The correct legal standard for obviousness is *objective* in  
14 nature, rather than subjective. Patentability is to be assessed from the perspective of the  
15 hypothetical person of ordinary skill in the art; not from the perspective of the inventors, who are  
16 presumed to be persons of extraordinary skill. Thus, the Examiner's consideration of what  
17 Appellants regarded as a solution to the problem of bead loss or other subjective motivations is  
18 completely irrelevant, and have been improperly interjected into this obviousness determination.  
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## II. CONCLUSION

For the reasons above and those articulated in the Appeal Brief mailed December 16, 2007, Appellants maintain that the Examiner did not articulate a prima facie basis to deny patentability to the claimed invention under 35 USC §103(a) for lack of requisite realistic motivation. It is further maintained that the Examiner has not given weight to the significant teaching away of Rothberg et al. as confirmed by Rothberg et al's own admissions during the prosecution of the cited patent's progeny applications. Appellants, therefore, submit that the Examiner's rejection of the appealed claims under 35 USC §103(a) is not procedurally or legally viable and, hence, solicit reversal thereof.

Appellants submit that the Examiner's rejections under 35 USC §103(a) are factually and legally erroneous and, hence, solicit the Honorable Board to reverse the Examiner's rejections of the appealed claims. Appellants are separately filing a Request for Oral Hearing pursuant to 37 C.F.R. §41.47.

To the extent necessary, a petition for an extension of time under 37 CFR. 1.136 is hereby made. Please charge any shortage in fees due under 37 CFR. 1.17 and 41.20, and in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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